

Submitted herewith is the Declaration of Dr. Fabrizio Samaritani (the “Samaritani Declaration”). The Samaritani Declaration is provided to verify the state of the art, and the level of skill in the art, at the time of the making of the present invention. The Samaritani Declaration further provides expert commentary on the cited art and how it would be viewed by a person skilled in the art. To understand the present invention in a proper perspective, and to avoid the application of improper hindsight, it is necessary to consider the state of the art at the time the invention was made.

As for all pharmaceutical preparations, FSH must be provided to patients in a manner that assures that the FSH remains preserved and stable up until use. For more than thirty years, the art met these requirements by providing FSH formulations as lyophilized powders. Samaritani Declaration, ¶ 10. Stable and preserved liquid preparations were not commercially available. As a consequence, patients were required to reconstitute the lyophilized powders for each use - which for some regimens meant reconstituting the powders for as many as 14 consecutive days. Samaritani Declaration, ¶ 11. Providing FSH in such an inconvenient form was a long-standing problem which the art struggled to overcome, and there remained a substantial need for a multi-use liquid formulation. Samaritani Declaration, ¶ 10 and 11.

One of the primary difficulties in solving the problem was that formulating a stable and preserved liquid form of FSH is a very difficult proposition for many reasons. FSH is a dimeric protein that is particularly unstable and sensitive to destabilizing effects/additives. At low concentrations FSH tends to dissociate and at high concentrations FSH tends to aggregate. Samaritani Declaration, ¶ 12. Moreover, any excipient present in a formulation has the potential of influencing the dissociation and/or aggregation of FSH. The problem is even greater for

recombinant FSH, which persons skilled in the art understand is particularly unstable.

Samaritani Declaration, ¶ 12.

The formulating of FSH is therefore highly unpredictable. Each added excipient has the potential of having a deleterious effect on the solution. The relation between protein structure and stability remains obscure, and the same is true as to potential interactions with or between other components such as preservatives and surfactants. Samaritani Declaration, ¶ 13. The presence of a second dimeric protein LH, as contemplated by a number of the pending claims, further increases the unpredictability of achieving a formulation in which the proteins remain stable and viable. Samaritani Declaration, ¶ 13. Precipitation is yet another example of a problem presented by incompatible components. Samaritani Declaration, ¶ 14. The difficulty of successfully formulating a stable and preserved liquid form of FSH is confirmed by the cited Hoffman and Skrabanja references. Samaritani Declaration, ¶ 16, 18 and 19.

The cited references do not anticipate or make obvious the claimed invention. Hoffman deals with the use of particular preservatives to inhibit bacterial growth. Hoffman merely recites an extensive list of other possible constituents to be included in an FSH formulation, while at the same time recognizing the difficulty in finding compatible components for an FSH solution. Samaritani Declaration, ¶ 16. Skrabanja relies on both a polycarboxylic acid (or a salt thereof) and thioether in order to stabilize an FSH formulation. Samaritani Declaration, ¶ 20. The references therefore take very different approaches to stabilizing FSH formulations, and a person of ordinary skill in the art would not have had any motivation to combine these references. Samaritani Declaration, ¶ 21 and 22. There is no teaching, motivation or suggestion to combine Hoffman and Skrabanja in the manner suggested, and there would be no expectation of success in making such a combination. Samaritani Declaration, ¶ 15, 17 and 23. Moreover, a

combination of Hoffman and Skrabanja made by a person of ordinary skill in the art at the time the invention was made, and without benefit of hindsight, would not have resulted in the claimed invention. Samaritani Declaration, ¶¶25 and 26.

The heart of the basic requirements for showing a *prima facie* case of obviousness is one of predictability. A number of “exemplary rationales” for supporting an obviousness rejection are set forth in MPEP 2143. Each one of these rationales uses the word “predictable” or conveys a similar notion. The first rationale, for example, is the combining of prior art elements according to known methods to yield “predictable results”. In contrast, for the present invention a person of ordinary skill in the art would not have considered it predictable, at the time of making the invention, to formulate a stable and preserved liquid formulation of FSH. Samaritani Declaration, ¶¶ 9, 13, 15, 27 and 28. Given the many difficulties in achieving a stable and preserved liquid formulation of FSH, it can not be said that the combination of Hoffman and Skrabanja in the particular manner suggested would have carried with it an expectation of success. Samaritani Declaration, ¶¶ 15 and 28.

The present invention is therefore shown to be a novel and unobvious approach to providing a liquid FSH formulation. The unique combination of components, as recited in the claims, provides a preserved and stable formulation which does not result in precipitation and which is suitable as a multi-use medication. Samaritani Declaration, ¶¶ 8 and 9. Such a formulation was not provided in the art for more than thirty years. If it was so easy, pharmaceutical companies would have rushed such a product to market in order to alleviate the extreme burden imposed by the existing, lyophilized preparations.

Reconsideration of the above-identified patent application, as previously amended and in view of the foregoing, is respectfully requested. An action on the merits and allowance of the

claims is solicited. If the Examiner believes that it would expedite examination of this case, the Examiner is requested to contact the undersigned directly.

Respectfully submitted,

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